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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 311/16, C07D 207/09, 217/06, 295/12, 295/18, 295/22, A61K 31/18

A1

(11) International Publication Number: WO 99/36398

(43) International Publication Date: 22 July 1999 (22.07.99)

(21) International Application Number: PCT/GB99/00099

(22) International Filing Date: 13 January 1999 (13.01.99)

(30) Priority Data:
9800750.3 14 January 1998 (14.01.98) GB

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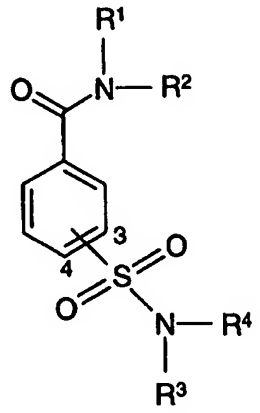
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AMINOSULPHONYLBENZAMIDE DERIVATIVES AS MODULATORS OF THE ACTIVITY OF NEURONAL CALCIUM CHANNELS



(I)

(57) Abstract

A pharmaceutical compound of formula (I) in which the aminosulfonyl group is attached at the 3– or 4–position, and in which R^1 is hydrogen, C_{1-6} Alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl–C_{1-4} alkyl or optionally substituted phenyl–C_{1-4} alkyl, R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl–C_{1-4} alkyl, optionally substituted phenyl–C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl–C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl–C_{1-4} alkyl, or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group; or a salt thereof.

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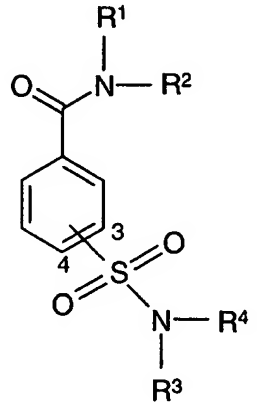
AMINOSULPHONYLBENZAMIDE DERIVATIVES AS MODULATORS OF THE ACTIVITY OF NEURONAL CALCIUM CHANNELS

This invention relates to novel chemical compounds and their use as pharmaceuticals.

It is well known that chemical compounds which modulate the activity of neuronal calcium channels are potentially useful in treating disorders of the central nervous system.

The compounds of the invention have the following general formula:



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group;

or a salt thereof.

The compounds of the invention have been found to be active in tests that show modulation of voltage-dependent calcium channels, and are thus indicated for use in the treatment of diseases in which such modulation is beneficial, in particular diseases of the central nervous system.

In the above formula (I), a C_{1-6} alkyl group includes methyl, ethyl, propyl, isopropyl, butyl, tert. butyl and hexyl, and is preferably methyl or ethyl. A substituted phenyl group is phenyl substituted with one or more, for example one to three, substituents selected from, for example C_{1-4} alkyl, especially methyl, C_{1-4} alkoxy, especially methoxy and ethoxy, hydroxy, nitro, cyano, halo, especially chloro or fluoro, trihalomethyl, especially trifluoromethyl, carboxy and C_{1-4} alkoxy-carbonyl. A halo atom is preferably chlorine, bromine or fluorine. A substituted phenyl group preferably has one to three substituents selected from hydroxy, C_{1-4} alkyl, halo, nitro and trifluoromethyl. An optionally substituted phenyl-C_{1-4} alkyl group is preferably of the formula R-$(CH_2)_n$- where R is optionally substituted phenyl and n is 1 to 4, but the linking chain can also

be branched alkylene. A C_{3-10} cycloalkyl group is preferably, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and these groups may optionally be substituted by one or two C_{1-4} alkyl, especially methyl, substituents. A C_{3-10} cycloalkyl-C_{1-4} alkyl group is one such cycloalkyl group attached to a C_{1-4} alkyl, and is preferably of the formula $R-(CH_2)_n-$ where R is cycloalkyl and n is 1 to 4. When R^3 or R^4 are C_{1-6} alkyl they are preferably C_{3-6} alkyl.

The groups R^1 and R^2, R^3 and R^4, and R^5 and R^6, can form a carbocyclic ring with the nitrogen to which they are attached and optionally also contain an oxygen atom or an additional nitrogen. Preferred examples, including the nitrogen of the amino sulfonyl group, are pyrrolidino, piperazino, morpholino and especially 3,5-dimethylpiperidino.

A particular group of compounds of the invention is one of formula (I) in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4

together with the nitrogen atom to which they are attached, form a carbocyclic group as defined above.

In a preferred group of compounds R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 is in addition hydrogen.

It is preferred that R^1 is hydrogen. Furthermore, R^3 and R^4, which can be the same or different, are preferably C_{1-4} alkyl. It is further preferred that R^2 is optionally substituted phenyl-C_{1-4} alkyl.

A further preferred group of compounds is one of formula (I) in which R^2 is $-(CH_2)_2NR^5R^6$.

A further preferred group of compounds is one of formula (I) in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

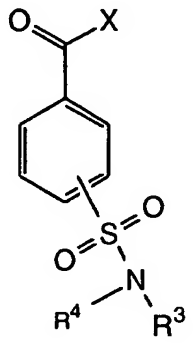
It will be appreciated that the compounds of the invention can contain one or more asymmetric carbon atom which gives rise to enantiomers. The compounds can be prepared as racemates or can be made from enantiomeric intermediates. Both racemates and enantiomers form part of the present invention.

It will also be understood that salts of the compounds of the invention can be prepared and such salts are included in the invention. They can be any of the well known acid addition salts. Acid addition salts are preferably the pharmaceutically acceptable non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example glycollic, maleic, fumaric, malic,oxalic, tartaric, citric, salicylic or o-acetoxybenzoic acids, or organic sulfonic acids, methane sulfonic, 2-hydroxyethane sulfonic, toluene-p-sulfonic or naphthalene-2-sulfonic acids.

In addition to pharmaceutically-acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically-

acceptable, salts, or are useful for identification, characterisation or purification.

The invention also includes a process for producing the compounds of formula (I) above which comprises reacting a compound of the formula:



(II)

where X is a leaving group such as, for example, halo or hydroxy, with an amine of the formula HNR^1R^2.

The reaction is preferably carried out in an organic solvent such as, for example, chloroform or acetonitrile, at a temperature of from 0° C. to 100° C. such as, for example, ambient temperature.

Intermediate compounds of formula (II) are known in the art and can be prepared readily by known methods. When

an acid halide is employed (X is halo such as, for example, chloro), the reaction is preferably carried out in the presence of a solid phase scavenger to absorb the acid liberated by the reaction. When the free acid is employed (X is hydroxy), a condensing reagent such as, for example, dimethylaminopropyl-ethylcarbodiimide can be employed.

Amine reactants of the formula HNR^1R^2 are also well known and can be prepared readily by known methods. Those in which R^2 is $-(CH_2)_2NR^5R^6$ can, for example, be prepared by reductive amination, that is, by reacting the appropriate diamine with an aldehyde in reducing conditions.

Alternatively, such compounds in which R is $-(CH_2)_2NR^5R^6$ can be prepared by alkylation of the corresponding compound of formula (I) in which R^1 is hydrogen.

As mentioned above, the compounds of the invention are active in tests that indicate their utility in the treatment of diseases of the central nervous system. The compounds modulate the activity of calcium channels and, in particular, they block voltage sensitive calcium

channels as determined in a test based on Boot J. R., et al., Specificity of autoantibodies in the Lambert-Eaton Myasthenic Syndrome, Ann NY Acad. Sci. (1997), in which measurements of calcium flux using calcium sensitive dyes are made. Compounds described in the following Examples were found to inhibit voltage-dependent calcium channels in cloned human cell lines expressing specific voltage-dependent calcium channels with an IC_{50} of less than 10 μM.

The compounds of the invention are thus indicated for use in the treatment of anoxia, ischaemia, stroke and heart failure, migraine, diabetes, cognitive impairment, pain, epilepsy, traumatic head or spinal injury, AIDS related dementia and blindness, amnesia, neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases and age-related memory disorders, Down's syndrome, mood disorders, drug or alcohol addition withdrawal, nausea from chemotherapy, and carbon monoxide or cyanide poisoning.

The invention also includes a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in association with the compound of the invention or a pharmaceutically acceptable salt or ester thereof.

The compound may be administered by various routes, for example by the oral or rectal route, topically or parenterally, for example by injection or infusion, being usually employed in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, ointments containing, for example, up to 10% by weight of the compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydrobenzoate, talc magnesium stearate and mineral oil. The compositions of the injection may, as is well known

in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Where the compositions are formulated in unit dosage form, it is preferred that each unit dosage form contains from 5 mg to 500 mg. The term 'unit dosage form' refers to physically discrete units suitable as unit dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier.

The active compound is effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.5 to 300 mg/kg, more usually in the range of from 5 to 100 mg/kg. However, it will be understood that the amount administered will be determined by the physician in the light of the relevant circumstances including the conditions to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The invention is illustrated by the following Preparations and Examples.

EXAMPLE 1

4-(N,N-dipropylaminosulfonyl)-N-benzyl-benzamide

To 50-100 mg polyvinylpyridine was added a 25 mM solution of benzylamine in chloroform (1 ml), followed by a 37.5 mM solution of 4-(N,N-dipropylaminosulfonyl)-benzoyl chloride in chloroform (1 ml). The mixture was shaken at room temperature for 4 hours. Aminomethylpolystyrene (100 mg, 0.1 mmole) was added and shaking continued for a further 16.5 hours. The mixture was then filtered and the resin washed with chloroform (2 x 2 ml). The combined filtrates were vacuum evaporated to give the required product. (TS-MS: m/z 375, $[M+H]^+$)

The following compounds were similarly prepared (mass spectrum values are given in brackets).

	Thermospray Mass Spectrum values
4-(N,N-Dipropylaminosulfonyl)-N,N-dibenzyl-benzamide	(465)

4-(N,N-Dipropylaminosulfonyl)-N-3,4-dimethoxybenzyl-benzamide (435)

4-(N,N-Dipropylaminosulfonyl)-N-3,5-dimethoxybenzyl-benzamide (435)

4-(N,N-Dipropylaminosulfonyl)-N-3-methoxybenzyl-benzamide (405)

4-(N,N-Dipropylaminosulfonyl)-N-3,4,5-trimethoxybenzyl-benzamide (465)

4-(N,N-Dipropylaminosulfonyl)-N-4-chlorobenzyl-benzamide (409/410)

4-(N,N-Dipropylaminosulfonyl)-N-4-trifluoromethylbenzyl-benzamide (443)

4-(N,N-Dipropylaminosulfonyl)-N-4-dimethylaminobenzyl-benzamide (418)

4-(N,N-Dipropylaminosulfonyl)-N-4-methylbenzyl-benzamide (389)

4-(N,N-Dipropylaminosulfonyl)-N-3-chlorobenzyl-benzamide (409/410)

4-(N,N-Dipropylaminosulfonyl)-N-3-methylbenzyl-benzamide (389)

4-(N,N-Dipropylaminosulfonyl)-N-3-trifluoromethylbenzyl-benzamide (443)

4-(N,N-Dipropylaminosulfonyl)-N-3.5-difluoromethylbenzyl-benzamide (411)

4-(N,N-Dipropylaminosulfonyl)-N-2,6-dimethoxybenzyl-benzamide (435)

4-(N,N-Dipropylaminosulfonyl)-N-2-methylbenzyl-benzamide (389)

4-(N,N-Dipropylaminosulfonyl)-N-2-chlorobenzyl-benzamide (409/410)

4-(N,N-Dipropylaminosulfonyl)-N-2-methoxybenzyl-benzamide (405)

4-(N,N-Dipropylaminosulfonyl)-N-2-trifluoromethylbenzyl-benzamide (443)

4-(N,N-Dipropylaminosulfonyl)-N-3,4-dimethylbenzyl-benzamide (403)

4-(N,N-Dipropylaminosulfonyl)-N-2,6-dichlorobenzyl-benzamide (444)

4-(N,N-Dipropylaminosulfonyl)-N-4-methoxyphenethyl-benzamide (419)

4-(N,N-Dipropylaminosulfonyl)-N-phenethyl-benzamide (389)

4-(N,N-Dipropylaminosulfonyl)-N-3-methoxyphenethyl-benzamide (419)

4-(N,N-Dipropylaminosulfonyl)-N-4-nitrophenethyl-benzamide (434)

4-(N,N-Dipropylaminosulfonyl)-N-2-phenylpropyl-benzamide (403)

4-(N,N-Dipropylaminosulfonyl)-N-4-chlorophenethyl-benzamide (423/424)

4-(N,N-Dipropylaminosulfonyl)-N-4-methylphenethyl-benzamide (403)

4-(N,N-Dipropylaminosulfonyl)-N-2-methoxyphenethyl-benzamide (419)

4-(N,N-Dipropylaminosulfonyl)-N-2-chlorophenethyl-benzamide (423/424)

4-(N,N-Dipropylaminosulfonyl)-N-3-trifluoromethylphenethyl-benzamide (457)

4-(N,N-Dipropylaminosulfonyl)-N-hexyl-benzamide (369)

4-(N,N-Dipropylaminosulfonyl)-N-2-methylbutyl-benzamide (355)

4-(4-N,N-Dipropylaminosulfonyl)benzoylmorpholine (355)

2-(4-N,N-Dipropylaminosulfonyl)benzoyl-6,7-dimethoxy-tetra-hydroisoquinoline (461)

4-(N,N-Dipropylaminosulfonyl)-N-3-methoxypropyl-benzamide (357)

4-(N,N-Dipropylaminosulfonyl)-N-2-methylpropyl-benzamide (355)

4-(N,N-Dipropylaminosulfonyl)-N-cyclohexylmethyl-benzamide (381)

4-(N,N-Dipropylaminosulfonyl)-N-cyclohexyl-benzamide (367)

4-(N,N-Dipropylaminosulfonyl)-N-cyclopentyl-benzamide (353)

4-(N,N-Dipropylaminosulfonyl)-N-pentyl-benzamide (355)

4-(N,N-Dipropylaminosulfonyl)-N-3-methylbutyl-benzamide (355)

4-(N,N-Dipropylaminosulfonyl)-N-3-phenylpropyl-benzamide (403)

4-(N,N-Dipropylaminosulfonyl)-N-4-*tert*.butylcyclohexyl-benzamide (423)

4-(N,N-Dipropylaminosulfonyl)-N-4-phenylbutyl-benzamide (417)

4-(N,N-Dipropylaminosulfonyl)-N-1-aminopropylpyrrolidine (396)

4-(N,N-Dipropylaminosulfonyl)-N-3-methylcyclohexyl-benzamide (381)

4-(N,N-Dipropylaminosulfonyl)-N-1-benzyl-4-aminopoperidine (458)

4-(N,N-Dipropylaminosulfonyl)-N-cyclopropylmethyl-benzamide (339)

4-(N,N-Dipropylaminosulfonyl)-N-butyl-benzamide (341)

EXAMPLE 2

4-(N,N-dipropylaminosulfonyl)-N-4-methoxybenzyl-benzamide

A mixture of a 75 mM solution of 4-methoxybenzylamine in chloroform (0.5 ml), a 75 mM solution of N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in chloroform (0.5 ml) and a 50 mM

solution of 4-(N,N-dipropylaminosulfonyl)-benzoic acid in chloroform (0.5 ml) was stirred at room temperature for 17 hours. Methanol (0.5 ml) was added with stirring and the solution applied to a methanol-washed 500 mg SCX solid phase extraction (SPE) cartridge. The cartridge was washed with methanol (4 ml) and the combined eluates vacuum evaporated to give the required product. (TS-MS: m/z 405, $[M+H]^+$).

EXAMPLE 3

4-(N,N-dibutylaminosulfonyl)-N-4-methoxybenzyl-benzamide

A mixture of a 200 mM solution of dibutylamine in acetonitrile (0.5 ml) and a 25 mM solution of 4-chlorosulfonylbenzoic acid in acetonitrile (1 ml) was stirred at room temperature for 18 hours. Methanol (1 ml) was then added with stirring and the solution applied to a methanol-washed 500 mg SCX SPE cartridge. The cartridge was washed with methanol (4 ml) and the combined eluates vacuum evaporated. The residue was dissolved in dichloromethane (1 ml) and a 75 mM solution of 4-methoxybenzylamine in chloroform (0.5 ml) and a 75 mM solution of N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in chloroform (0.5 ml)

added. This mixture was stirred at room temperature for 17 hours. Methanol (0.5 ml) was added with stirring and the solution applied to a methanol-washed 500 mg SCX SPE cartridge. The cartridge was washed with methanol (4 ml) and the combined eluates vacuum evaporated to give the required product. (TS-MS: m/z 433, $[M+H]^+$)

The following compounds were prepared similarly.

	Thermospray Mass Spectrum values
4-(N-pentylaminosulfonyl)-N-4-methoxybenzyl-benzamide	(391)
4-[N-(3-methylcyclohexyl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(417)
4-[(N-butyl-N-propyl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(419)
4-[N-(3,5-dimethylpiperidin-1-yl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(417)
4-[(N-diisobutyl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(433)
4-[N-(3-methylpiperidin-1-yl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(403)
4-[(N-methylbutyl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(405)
4-[(4-methylpiperidin-1-yl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(403)
4-[(3,3-dimethylpiperidin-1-yl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(417)
4-[(N-cyclopropyl-N-propylmethyl)aminosulfonyl]-N-4-methoxybenzyl-benzamide	(417)

EXAMPLE 4

3-(N,N-dipropylaminosulfonyl)-N-3,4-dimethoxyphenethyl-benzamide

A mixture of a 200 mM solution of dipropylamine in acetonitrile (0.5 ml) and a 25 mM solution of 3-chlorosulfonylbenzoic acid in acetonitrile (1 ml) was stirred at room temperature for 18 hours. Methanol (1 ml) was then added with stirring and the solution applied to a methanol-washed 500 mg SCX SPE cartridge. The cartridge was washed with methanol (4 ml) and the combined eluates vacuum evaporated. The residue was dissolved in dichloromethane (1 ml) and a 75 mM solution of 3,4-dimethoxyphenethylamine in chloroform (0.5 ml) and a 75 mM solution of N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in chloroform (0.5 ml) added. This mixture was stirred at room temperature for 17 hours. Methanol (0.5 ml) was added with stirring and the solution applied to a methanol-washed 500 mg SCX SPE cartridge. The cartridge was washed with methanol (4 ml) and the combined eluates vacuum evaporated to give the required product. (TS-MS: m/z 449, $[M+H]^+$)

EXAMPLE 5

(1) 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid

To a stirred solution of di-n-propylamine (3.03 g, 0.03 mole) in dry tetrahydrofuran (20 ml) at 0° C.

(ice/salt bath), was added 4-chlorosulfonylbenzoic acid (2.2 g, 0.01 mole). Stirring was continued for 1 hour. Ice water was added cautiously and the reaction made acid with 2NHCl. The 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid was collected by filtration as a white solid which was dried *in vacuo* at 40° C.

Similarly prepared were:

3-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid

4-[(N-phenyl-N-n-propylamino)sulfonyl]-benzoic acid

4-[(N-phenyl-N-n-allylamino)sulfonyl]-benzoic acid

3-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-benzoic acid

4-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-benzoic acid

4-[(N-phenyl-N-n-butylamino)sulfonyl]-benzoic acid

3-[(N-phenyl-N-n-propylamino)sulfonyl]-benzoic acid

3-[N-(3-ethylpiperidin-1-yl)sulfonyl]-benzoic acid

3-[(N-phenyl-N-methyl)sulfonyl]-benzoic acid

4-[N-(3-methylpiperidin-1-yl)sulfonyl]-benzoic acid

(2) 4-[(N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide

To a solution of 4-[(N,N-di-n-propylamino)sulfonyl]-benzoic acid (2.85 g, 0.01 mole) in dry dichloromethane (ml) at 0° C. was added oxalyl chloride (2.54 g, 0.02 mole) and dimethylformamide (4 drops). The reaction mixture was stirred for 2 hours. The reaction was evaporated to dryness *in vacuo*. The resulting acid chloride was added to a stirred solution of *p*-methoxybenzylamine (1.51 g, 0.011 mole) and triethylamine (1.11 g, 0.011 mole) in dry tetrahydrofuran (25 ml) at 0-5° C. After stirring for 4 hours the reaction was poured into ice water and extracted with ethyl acetate. The solvent was washed with brine, dried and evaporated to dryness *in vacuo*. Chromatography on flash silica using 10% ethyl acetate/dichloromethane gave 4-{(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide as a white solid. M.p. 132-134° C.

Similarly prepared were:

3-[(N,N-di-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide. M.p. 132-134° C.

4-[(N-phenyl-N-n-propylamino)sulfonyl]-N-4-methoxybenzyl-benzamide. M.p. 112-114° C.

4-[(N-phenyl-N-n-butylamino)sulfonyl]-N-n-hexyl-benzamide. M.p. 84-86° C.

4-[(N-phenyl-N-n-allylamino)sulfonyl]-N-n-hexyl-benzamide. M.p. 90-92° C.

4-[(N-phenyl-N-n-propylamino)sulfonyl]-N-n-hexyl-benzamide. M.p. 92-94° C.

3-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 125° C.

4-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 138-140° C.

3-[(N,N-di-n-propylamino)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 84-86° C.

N-methyl-3-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. <50° C.

N-benzyl-3-[N-(3,3-dimethylpiperidin-1-yl)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 112° C.

4-[(N-phenyl-N-n-butylamino)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 128-130° C.

3-[(N-phenyl-N-n-propylamino)sulfonyl]-N-4-fluorobenzyl-benzamide. M.p. 99° C.

4-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-(2-{[(4-fluorophenyl)methyl] amino}ethyl)benzamide. Maleate. M.p. 132-134° C.

3-[N-(3-ethylpiperidin-1-yl)sulfonyl]-N-4-fluorobenzyl-benzamide. 405$(M+H)^+$

N-[2-(dimethylamino)ethyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-4-fluorobenzyl-benzamide maleate. M.p. 126° C.

N-[2-(dimethylamino)ethyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-cyclohexylmethyl-benzamide. M.p. 122° C.

N-[2-(dimethylamino)ethyl]-4-[(N-phenyl-N-n-propylamino)sulfonyl]-*N*-cyclohexylmethyl-benzamide maleate. M.p. 140-142° C.

N-[2-(pyrrolidino)ethyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-isoamyl-benzamide hydrochloride. M.p. 179° C.

N-[2-(pyrrolidino)ethyl]-4-[(3-ethylpiperidin-1-yl)sulfonyl]-*N*-isoamyl-benzamide malea. M.p. 166-168° C.

N-[3-(pyrrolidino)propyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-isoamyl-benzamide hydrochloride. M.p. 155° C.

N-[3-(pyrrolidino)propyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-cyclohexylmethyl-benzamide. M.p. 124° C.

N-[2-(*N*-methyl-pyrrolidin-2-yl)ethyl]-3-[(3,3-dimethylpiperidin-1-yl)sulfonyl]-*N*-isoamyl-benzamide maleate. M.p. 115-117° C.

N-[2-(piperidin-1-yl)ethyl]-3-[(3-methylpiperidin-1-yl)sulfonyl]-*N*-(2-4-methoxyphenethyl)-benzamide. M.p. 210° C.

N-[2-(piperidin-1-yl)ethyl]-3-[(3-methylpiperidin-1-yl)sulfonyl]-*N*-(2-4-methoxyphenethyl)-benzamide hydrochloride. M.p. 205° C.

The following Examples illustrate typical formulations containing a compound of the invention.

EXAMPLE 6

Tablets each containing 10 mg of active ingredient are made up as follows:

Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which,

after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

EXAMPLE 7

Capsules each containing 20 mg of active ingredient are made as follows:

Active ingredient	20 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 8

Capsules each containing 20 mg of medicament are made as follows:

Active ingredient	20 mg
Lactose	171 mg
Sodium lauryl sulphate	2 mg
Sodium starch glycollate	6 mg
Magnesium stearate	1 mg
	200 mg

The active ingredient, lactose, sodium lauryl sulphate and sodium starch glycollate are mixed thoroughly. The blend is mixed with the magnesium stearate and filled into hard gelatine capsules in 200 mg quantities.

EXAMPLE 9

Tablets each containing 20 mg and medicaments are made as follows:

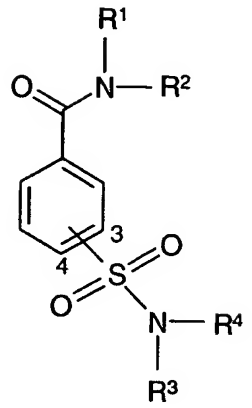
Active ingredient	20 mg
Lactose	103 mg
Microcrystalline cellulose	150 mg
Hydroxypropylmethylcellulose	15 mg
Sodium starch glycollate	9 mg
Magnesium stearate	3 mg

300 mg

The active ingredient, lactose, microcrystalline cellulose, sodium starch glycollate and hydroxypropylmethylcellulose are passed through a sieve and blended together. Water is added to the blended powders to form a damp mass. The damp mass is passed through a coarse screen, dried, then re-screened. The dried granules are mixed with the magnesium stearate and compressed into tablets of 300 mg weight.

CLAIMS

1. A compound of the formula



(I)

in which the aminosulfonyl group is attached at the 3- or 4-position, and in which

R^1 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl,

R^2 is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, optionally substituted phenyl-C_{1-4} alkyl or $-(CH_2)_2NR^5R^6$ where R^5 and R^6 are each hydrogen or C_{1-6} alkyl, and

R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{3-6} alkenyl, optionally substituted phenyl or optionally substituted phenyl-C_{1-4} alkyl,

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, together with the nitrogen atom to which they are attached, form a carbocyclic group containing 4 to 7 carbon atoms optionally substituted with one to three methyl or ethyl groups and optionally containing an oxygen atom or a further nitrogen atom, said carbocyclic group being optionally fused to an optionally substituted phenyl group;

or a salt thereof.

2. A compound according to Claim 1 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen, or R^1 and R^2, or R^3 and R^4 together with the nitrogen atom to which they are attached, form a carbocyclic group.

3. A compound according to Claim 2 in which R^1, R^2, R^3 and R^4 are each C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl or optionally substituted phenyl-C_{1-4} alkyl, and R^1 can in addition be hydrogen.

4. A compound according to Claim 3 in which R^1 is hydrogen, R^2 is optionally substituted phenyl-C_{1-4} alkyl and R^3 and R^4 are C_{1-6} alkyl.

5. A compound according to Claim 1 in which R^2 is $-(CH_2)_2NR^5R^6$.

6. A compound according to Claim 1 or 5 in which R^3 or R^4 is C_{3-6} alkyl or when R^3 and R^4 are taken together with the nitrogen atom they form a piperidine ring which is substituted at the 3- and/or 5-positions with one or two methyl or ethyl substituents.

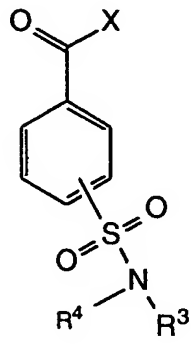
7. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 6 or a

pharmaceutically acceptable salt thereof, together with a diluent or carrier therefor.

8. A compound according to any of Claims 1 to 6, for use as a pharmaceutical.

9. Use of a compound according to any of Claims 1 to 6, in the manufacture of a medicament for treating a disease of the central nervous system.

10. A process for producing a compound according to Claim 1, which comprises reacting a compound of the formula



(II)

where X is a leaving group, with an amine of the formula HNR^1R^2.

INTERNATIONAL SEARCH REPORT

Intl Jonal Application No
PCT/GB 99/00099

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/16 C07D207/09 C07D217/06 C07D295/12 C07D295/18
C07D295/22 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	P. BEAK, ET AL.: "The tertiary amide as an effective director of ortho lithiation" JOURNAL OF ORGANIC CHEMISTRY, vol. 47, no. 1, 1 January 1982, pages 34-46, XP002100405 Washington, DC, US see compound 22 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	06/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

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INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
PCT/GB 99/00099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	K. YONEYAMA, ET AL.: "Phytotoxic activity of N-benzylbenzenesulphonamides" AGRICULTURAL AND BIOLOGICAL CHEMISTRY, vol. 48, no. 2, February 1984, pages 491-498, XP002100406 New York, US see page 493, lines 29-34 and compound II where R1,Y = H, R2 = Me, X = CONMe2 ---	1-3
A	US 5 591 754 A (H.-J. LANG, ET AL.) 7 January 1997 see column 1 - column 3 -----	1-10

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Information on patent family members

Inte ional Application No
PCT/GB 99/00099

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